REMARKS

Applicant encloses an appendix that shows the changes made to the title and to claim 28 by the current amendment. Claim 28 has been amended and claim 35 has been cancelled without prejudice or disclaimer. New claims 42-46 have been added. Support for new claim 42 can be found in the specification, e.g., at page 11, lines 6-8, and at page 10, lines 11-13. Support for new claims 43 and 46 can be found in the specification, e.g., at page 13, lines 11-14 and lines 21-22. Support for new claims 44 and 45 can be found in the specification, e.g., at page 13, lines 21-26. Following entry of this amendment, claims 28, 29, 31, and 36-46 are pending in the application.

Claim 28 has been amended to remove the recitation of SEQ ID NO: 11. Claims 29, 31, and 36-37 are dependent from claim 28, and therefore also no longer recite SEQ ID NO: 11. Claims 38-41 recite antibodies that specifically bind a polypeptide comprising amino acids 1 to 524 of SEQ ID NO: 11, and claims 42-46 recite antibodies that specifically bind a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 11. Thus, this response only addresses the rejections as they might apply to claims 38-46.

Specification

The Examiner stated that the disclosure is objected to because "Table 4 at page 25 contains several blurred entries" and appropriate correction is required. Action at page 2, Item No. 3. In the amendment above, applicants request that the previous page 25 be replaced with the enclosed substitute page 25. Substitute page 25 adds no new matter.

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Rejections under 35 U.S.C. § 101

The Examiner rejected claims 28, 29, 31, and 35-41 under 35 U.S.C. § 101 because the claimed invention allegedly is not supported by a specific or otherwise substantial asserted utility." Action at page 3, Item No. 5. The Examiner alleged that "the instant specification does not put forth what, in particular, the antibodies would be used to diagnose nor what particular activity they could be used to modulate." *Id.* The Examiner also indicated that "an assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would be a practical use of the material." *Id.* at page 4. Applicants respectfully traverse the rejection.

Evidence establishes that one skilled in the art would have recognized that antibodies according to claims 38-46 at least can be used to detect cancers that are characterized by overexpression of EPH family members, and to detect the predisposition to such cancers. For example, "it has been shown recently that overexpression of *Eph* in NIH3T3 cells results in tumorigenic ability in nude mice." Gilardi-Hebenstreit et al. (1992) *Oncogene* **7**: 2499-2506 at page 2504, left column; cited in the Information Disclosure Statement that was filed January 12, 2000 (I.D.S.). This evidence of tumorigenic capacity was borne out in another report, in which the authors studied EPH family member expression levels in human gastric cancers. Specifically, they found that expression of HEK5 (also called ERK) mRNA "was extremely higher in cancer tissues than in normal stomach in all cases examined." Iwase et al. (1993) *Biochem. Biophys. Res. Comm.* **194**: 698-705 at page 703; cited in the I.D.S. The authors concluded that receptor tyrosine kinase genes, including the

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HEK5 gene, "play pivotal roles in embryogenesis of stomach and ... the dysregulated expression of these genes have oncogenic potentials in the stomach." *Id.* at page 704. Another report found that ERK is overexpressed in 75% of gastric cancers tested, suggesting that "ERK plays some significant role in carcinogenesis in the stomach and other tissue." Kiyokawa et al. (1994) *Cancer Research* **54**: 3645-3650 at page 3645, Abstract. A copy of this document is enclosed.[1] Clearly, the correlation between EPH family members and cancer was known at the time of filing. Moreover, antibodies to EPH family members would have been recognized by one skilled in the art as having at least the substantial and credible utility of detecting such cancers and detecting the predisposition to such cancers.

Thus, applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 101.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner also rejected claims 28, 29, 31, 35-41 under 35 U.S.C. § 112, first paragraph. Action at page 5, Item No. 7. The Examiner alleged that "since the claimed invention is not supported by either a specific and substantial utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation." *Id.* Applicants respectfully traverse this rejection.

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[1] Although the publication date of Kiyokawa et al. (July 15, 1994) is after the filing date of the priority application, it was submitted prior to the priority filing date, on March 23, 1994. This document is therefore evidence that one skilled in the art at the time of filing would have recognized the utility of antibodies to EPH family members at the time of filing of the priority application (April 15, 1994).

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For the reasons set forth above, applicants assert that the invention has a utility that would have been recognized by one skilled in the art at the time of filing. Once a substantial and credible utility has been established, the corresponding rejection under 35 U.S.C. § 112, first paragraph, cannot properly be maintained. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection under 35 U.S.C. § 102

The Examiner rejected claims 28, 35, 38, and 39 under 35 U.S.C. § 102(b) as allegedly being anticipated by Pasquale (1991) *Cell Regulation* **2**: 523. Action at page 6, Item No. 9. The Examiner stated that "[t]he Cek5 polypeptide is 95% identical to the instant SEQ ID NO: 11, see the attached sequence alignment. Therefore, absent evidence to the contrary, the polyclonal antibodies disclosed by Pasquale are expected to specifically bind to the polypeptide of SEQ ID NO: 11." *Id.*

Solely to expedite prosecution and without acquiescing to the rejection, applicants have cancelled claim 35 and amended claim 28 to remove the recitation of SEQ ID NO: 11. New claim 42 has been added, which recites "a monoclonal antibody or fragment thereof that specifically binds a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 11." Applicants note that new claim 42 is derived from claim 29, which recites "an antibody of claim 28 which is a monoclonal antibody." Prior to amendment, claim 28 recited "an antibody or fragment thereof that specifically binds a polypeptide comprising an amino acid sequence as set forth in any of SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO: 15, or SEQ ID NO: 17." Therefore, because claim 29 was not rejected under 35 U.S.C. § 102(b), new claim 42 and the claims dependant from claim 42 (claims 43-45) should also not be rejected under 35 U.S.C. § 102(b).

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Claim 38 recites "an antibody or fragment thereof that specifically binds a polypeptide comprising any of: (a) amino acids 1 to 524 of SEQ ID NO: 11, (b) amino acids 1 to 547 of SEQ ID NO: 13, or (c) amino acids 1 to 547 of SEQ ID NO: 15." Claim 39 is dependent from claim 38 and recites an antibody or fragment thereof that "specifically binds a polypeptide comprising amino acids 1 to 524 of SEQ ID NO: 11." Amino acids 1 to 524 of SEQ ID NO: 11 comprise the extracellular domain of HEK5, as indicated in Example 3 of the specification, which states that "a construct of the HEK5 extracellular domain had a stop codon introduced after lysine at position 524 as shown in Figure 1." Specification at page 22, lines 9-12.

The polyclonal sera discussed in Pasquale were raised to a β-galactosidase fusion of amino acids 167-926 of Cek5, and to the 10 carboxy-terminal amino acids of Cek5. See Pasquale (1991) *Cell Regulation* **2**: 523-534 at page 525, right column, to 526, left column. Amino acids 167-926 of Cek5 encompass only 381 of the 548 amino acids of the extracellular domain, as well as all of the transmembrane domain and most of the intracellular domain. A polyclonal serum raised to a β-galactosidase fusion of amino acids 167-926 of CEK5 is not the same as an antibody that specifically binds to "a polypeptide comprising amino acids 1 to 524 of SEQ ID NO: 11." A large proportion of the antibodies in the polyclonal serum raised to the CEK5 fusion would recognize the transmembrane and intracellular domains and therefore would not "specifically bind" the extracellular domain of HEK5. In fact, it is not clear that *any* of the antibodies discussed by Pasquale specifically bind to the extracellular domain. It is well known in the art that some sequences are more antigenic than others. If the transmembrane and/or the intracellular domain is more antigenic than the extracellular domain, it is possible that

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none of the antibodies in the polyclonal serum specifically binds the extracellular domain.

The second polyclonal serum discussed by Pasquale was raised to the carboxy-terminal 10 amino acids of CEK5, which is amino acids 986-995 of CEK5, and corresponds to amino acids 961-970 of HEK5 in the alignment provided by the Examiner with the Office Action. As discussed above, claims 38 and 39 recite "an antibody that "specifically binds a polypeptide comprising amino acids 1 to 524 of SEQ ID NO: 11." Thus, there is no overlap between the antigen used to raise this polyclonal serum of Pasquale and the region of SEQ ID NO: 11 recited in the presently pending claims 38 and 39. The Examiner has not explained how the polyclonal serum raised to this carboxy-terminal region of CEK5 would "specifically bind a polypeptide comprising amino acids 1 to 524 of SEQ ID NO: 11." Thus, the Examiner fails to establish that Pasquale anticipates claims 38 and 39.

Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

Applicants respectfully assert that the present application is in condition for allowance and request that the Examiner issue a timely Notice of Allowance. If the Examiner does not consider the application to be allowable, the undersigned requests that, prior to taking action, the Examiner call her at (650) 849-6656 to set up an interview.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: January 24, 2002

By: _____
Rebecca B. Scarr
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APPENDIX

IN THE TITLE:

Please replace the title with the following title:

[NUCLEIC ACIDS ENCODING] ANTIBODIES TO EPH-LIKE RECEPTOR TYROSINE KINASES

IN THE CLAIMS:

Please amend claim 28 to read:

28. (Twice Amended) An antibody or fragment thereof that specifically binds a polypeptide comprising an amino acid sequence as set forth in any of [SEQ ID NO: 11,] SEQ ID NO: 13, SEQ ID NO: 15, or SEQ ID NO: 17.

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cytoplasmic domain anti-peptide antibodies, peptides were synthesized (see Table 4 for the sequences) and covalently coupled to keyhole limpet hemocyanin . The fusion proteins and coupled peptides were used as antigens in rabbits and antisera were generated and characterized as described (Harlow and Lane, 1988). Anti-peptide antibodies were affinity purified by using a SulfoLink kit (Pierce, Rockford IL).

TABLE 4

HEK Receptor Antigens

Receptor	Peptide Sequences		Amino Acids in Fusion Protein
HEK4	CLETQSKNGPVPV	(SEQ ID NO: 38)	22-159
HEK5	CRAQMNQIQSVEV	(SEQ ID NO: 39)	31-168
HEK7	CMKVQLVNGMVPL	(SEQ ID NO: 40)	335-545
HEK8	CMRTQMQQMHGRMVPV	(SEQ ID NO: 41)	27-188
HEK11	CQMLHLHGTGIQV	(SEQ ID NO: 42)	187-503

EXAMPLE 5

HEK/TrkB Chimeric Receptors

1. Generation of pSJA1 encoding rat trkB cytoplasmic domain.

All of the chimeric receptors are composed of the extracellular domain and the transmembrane region of one of the HEK receptors and the intracellular portion of rat trkB. To simplify each individual construction, an intermediate or parental plasmid, called RtrkB/AflII (or pSJA1), was generated. First, without altering the coded peptide sequence, an AflII site (CTTAAG) was introduced into position 2021 (cytosine at position 2021